Impact of bariatric surgery on carotid artery inflammation and the metabolic activity in different adipose tissues

OPEN

Impact of Bariatric Surgery on Carotid Artery Inflammation and the Metabolic Activity in Different Adipose Tissues

Jan Bucerius, MD, Guy H.E.J. Vijgen, MD, PhD, Boudewijn Brans, MD, PhD, Nicole D. Bouvy, MD, PhD, Matthias Bauwens, PhD, James H.F. Rudd, MD, PhD, Bas Havekes, MD, PhD, Zahi A. Fayad, PhD, Wouter D. van Marken Lichtenbelt, PhD, and Felix M. Mottaghy, MD

Abstract: In this study, we unravel a molecular imaging marker correlated with the known reduction of cardiovascular events (most commonly related to vulnerable plaques) in morbidly obese patients after bariatric surgery (BaS).

We prospectively imaged 10 morbidly obese subjects with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography before and 1 year after BaS. ^{18}F-FDG uptake—which is enhanced in inflamed, atherosclerotic vessels and in metabolically active adipose tissues—was quantified in the carotids, pericardial adipose tissue (PAT), visceral adipose tissue (VAT), as well as brown adipose tissue (BAT). The degree of carotid inflammation was compared to lean and overweight controls.

Carotid inflammation significantly declined leading to an ^{18}F-FDG uptake comparable to the 2 control groups. Metabolic activity significantly decreased in PAT and VAT and increased in BAT.

BaS leads to a normalization of carotid artery inflammation and a beneficial impact on the metabolic activity in PAT, VAT, and BAT that is related to the metabolic syndrome observed in this patient group.

(*Medicine* 94(20):e725)

Abbreviation: ^{18}F-FDG = 18F-fluorodeoxyglucose, BaS = bariatric surgery, BAT = brown adipose tissue, PAT = pericardial adipose tissue, SAT = subcutaneous adipose tissue, VAT = visceral adipose tissue.

INTRODUCTION

Most epidemiological studies demonstrate that obesity is associated with increased cardiovascular morbidity and mortality.[1,2] Unfortunately, >80% of even highly motivated obese patients are unable to achieve weight loss with dietary or lifestyle modifications alone.[3,4] Furthermore, medical treatment with anti-obesity drugs has shown either no effect on primary cardiovascular end points or even an increased risk of nonfatal myocardial infarction or stroke.[4–6] In contrast, several studies such as the Swedish obese subjects (SOS) trial revealed an association between bariatric surgery (BaS)-induced weight loss and a reduced number of cardiovascular events.[2,5,7,8] However, there is a lack of data about a potential direct impact of BaS on atherosclerotic changes in morbidly obese patients. In contrast, it is well known that the link between adipose tissue and vascular integrity, with proinflammatory changes in fat tissue, is related to vascular endothelial dysfunction.[9] This might at least partly explain the beneficial effects of BaS on cardiovascular events.[9] Supporting this pathophysiologic link, it became evident that expansion of abdominal visceral adipose tissue (VAT) and pericardial adipose tissue (PAT) associates with the metabolic syndrome and incident cardiovascular disease, mainly coronary artery disease and vascular calcification.[10–12] Additionally, recent work has better described the role and distribution of different types of fat. Human brown adipose tissue (BAT) is of special interest as it is known to be metabolically active by producing heat (thermogenesis) in response to cold conditions, which leads to enhanced energy expenditure and weight loss, with increased glucose and fatty acid uptake in BAT.[13–15] Accordingly, obese and overweight subjects were shown to have lower BAT activity.[13,15,16] Thus, BAT has emerged as a potential target for the treatment of obesity and obesity-associated cardiovascular diseases. However, whether BAT has a direct effect on vessel biology is not yet known.[16]

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) reflects the metabolic rate of glucose, a process known to be enhanced in inflamed vascular tissue. Accordingly, ^{18}F-FDG uptake was shown to be significantly associated with the degree of macrophage infiltration in vascular plaques.[17,18] Furthermore, ^{18}F-FDG PET demonstrated the presence of BAT in adult humans localized to areas close to the clavicles, axilla, aorta, cervical, vertebra, as well as the suprarenal regions and also seems to serve as a surrogate marker for increased metabolic activity in PAT and VAT.[14,15,19–21]

Editor: Daniel Pineiro.
Received: February 6, 2015; revised: March 4, 2015; accepted: March 7, 2015.
From the Department of Nuclear Medicine (JB, BB, MB, FMM); Cardiovascular Research Institute Maastricht (CARIM) (JB), Maastricht University Medical Center, Maastricht, The Netherlands; Department of Nuclear Medicine (JB, FMM), University Hospital, RWTH Aachen, Aachen, Germany; Department of Human Biology (GHEJV, MB, BH, WDVML), School for Nutrition, Toxicology, and Metabolism (NUTRIM); Department of General Surgery (GHEJV, NDB), Maastricht University Medical Center, Maastricht, The Netherlands; Division of Cardiovascular Medicine (JHFR), University of Cambridge, Cambridge, UK; Division of Endocrinology (BH), Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands; Translational and Molecular Imaging Institute (ZAF); Department of Radiology (ZAF); and Department of Cardiology, Zena and Michael A. Weiner Cardiovascular Institute, and Marie-Josée and Henry R. Kravis Cardiovascular Health Center (ZAF), Icahn School of Medicine at Mount Sinai, New York, USA.
Correspondence: Jan Bucerius, MD, Department of Nuclear Medicine and Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, P. Debyelaan 25, Maastricht 6229 HX, the Netherlands (e-mail: jan.bucerius@mumc.nl).
This work was supported by the Netherlands Science Foundation ZonMw Grant TOP 91209037 (WDvML) and the Stichting Weyerhorst, and partly supported by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre (JHFR).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000725

In this study, the ^{18}F-FDG PET technique was used to evaluate changes of the degree of carotid artery inflammation and the metabolic activity in PAT, VAT, and BAT in morbidly obese patients as depicted by ^{18}F-FDG-PET 1 year after BaS.

METHODS

Study Design

The study was conducted at the Maastricht University Medical Center (MUMC+), Maastricht, The Netherlands. All subjects gave written informed consent. The study was approved by the institutional review board and was performed according to the STROBE guidelines for cohort, case–control, and cross-sectional studies.[22]

All morbidly obese patients who presented at MUMC+ for planning of BaS were consecutively screened for inclusion in the study. Based on strict inclusion criteria, 2 male and 8 female patients, with a mean body mass index (BMI, kg/m^2) of 41.7 ± 4.34 were included in the study.[20] Exclusion criteria were known cardiovascular disease and risk factors for it, including hypertension, nicotine abuse, diabetes mellitus, and/or the use of statins or β-blockers, of which the latter is known to significantly reduce the metabolic activity of BAT. To exclude any impact of medication on vascular and fat tissue ^{18}F-FDG uptake, only patients without any change in their medications after BaS were further analyzed. However, none of the patients, except 1 patient requiring thyroid hormone substitution therapy, received any kind of medication throughout the study period. Most importantly, none of the patients received any kind of anti-inflammatory medication, either before or after BaS. ^{18}F-FDG PET/computed tomography (CT) data of lean (BMI < 25) or overweight (BMI $\geq 25 < 30$) healthy people, who participated in a previous study on BAT assessment, were reanalyzed in order to serve as controls for the vascular analyses in the morbidly obese patients.[15] Accordingly, data of people with BMI values $\geq$30 were excluded from serving as controls. As with the morbidly patients, none of the subject in the control groups suffered from cardiovascular disease or diabetes was known with nicotine abuse or received any medication with β-blockers or statins.

Study Protocol

^{18}F-FDG PET/CT

As earlier described in detail, a cooling protocol was applied to assure a standardized thermal situation for all included subjects.[15,19,20] In short, 1 hour of measuring under thermoneutral conditions (room temperature before weight loss: 22.8 ± 0.6°C, after weight loss: 23.7 ± 0.9°C; time (t)0–t60) was followed by 2 hours of individual mild cold (t60–t180). At the end of the first hour of cooling (t120), ^{18}F-FDG was injected. After the second hour of cooling, ^{18}F-FDG PET/CT imaging (Gemini TF PET/CT; Philips Healthcare Nederland B.V., Eindhoven, The Netherlands) was performed to quantify metabolically active BAT.

The PET/CT scanning protocol included confirmation of the serum glucose level (5.13–5.19 mmol/L) and the intravenous injection of a mean standard dose of 78.1–83.4 MBq (2.11–2.25 mCi) ^{18}F-FDG (Table 1). A low-dose noncontrast-enhanced CT scan (30 mAs) was performed for attenuation correction and localization of the ^{18}F-FDG uptake sites, immediately followed by the PET scan.[15] Total radiation dose from the PET/CT scan was approximately 2.8 mSv.

PET Image Analyses

An experienced reader (J.B.) who was blinded to the patient's characteristics and the date of the scan (presurgical or postsurgical ^{18}F-FDG PET/CT) analyzed all scans. Methodology for analysis and reproducibility of the measurements have been previously reported in part.[23,24]

Image Analysis of BAT

Methodology for BAT analysis has been previously reported.[15,19,20] In short, BAT activity measured as the maximal standardized uptake value (SUV_{max}) was quantified in the region of interest (ROI) in the BAT areas with a set threshold ($SUV_{max} \geq 1.0$). The SUV is the decay-corrected tissue concentration of ^{18}F-FDG in kBq/mL, adjusted for the injected ^{18}F-FDG dose and the body weight of the patient. Afterward, BAT SUV_{max} were corrected by the ^{18}F-FDG blood pool activity in the jugular veins (JVs) in order to obtain BAT target-to-background ratios (TBR_{max}). For evaluation of the blood pool activity, at least six 3 to 4-mm ROIs were placed in consecutive slices of the JV and averaged. The individual BAT TBR_{max} values obtained in each slice were then averaged to derive a $_{mean}TBR_{max}$ for the BAT (Figure 1C).

Image Analysis of PAT, VAT, and Subcutaneous Adipose Tissue

Image analysis was performed on a dedicated commercially available workstation (Extended Brilliance Workspace V4.5.3.40140; Philips Healthcare Nederland B.V., Eindhoven, The Netherlands).

In order to control for the specific metabolic activity of PAT and VAT as depicted by ^{18}F-FDG PET, we also analyzed the ^{18}F-FDG uptake in subcutaneous adipose tissue (SAT), which is known to be less metabolically active compared to VAT.[25,26] PAT, VAT, and SAT were identified based on a predefined range of Hounsfield units (−70 to −110) from CT images as previously described.[21] After fusion with the PET images, standard ROIs (7–15 mm, depending on the adipose tissue region) were placed on 3 consecutive slices whenever possible and SUV_{max} values across those slices were averaged (Figure 1A and B). SAT analysis was performed by placing ROIs in the presternal SAT. PAT ROIs were placed in the substernal mediastinal region of the chest cranial of the heart and therefore as far away as possible from the myocardium and the large vessels in order to exclude overspill from the myocardial and/or vascular ^{18}F-FDG uptake into the PAT region (Figure 1A). For VAT analysis, 3 consecutive standard ROIs were placed in the abdominal VAT above or below the kidneys to avoid overspill from the physiological ^{18}F-FDG uptake in the kidneys (Figure 1B). Overspill from intestinal, muscle, and/or vascular uptake into the abdominal adipose tissue was widely excluded by placing the ROIs at least 2 cm away from these structures. Again, SUV_{max} values across those slices were averaged. In general, PAT and VAT ROIs were not placed at all if an overspill from surrounding structures into the respective PAT or VAT region could not be excluded to the highest possible degree. As for the BAT SUV_{max} values, PAT, VAT, and SAT SUV_{max} were corrected by the ^{18}F-FDG blood pool activity in order to obtain PAT, VAT, and SAT TBR_{max} values, respectively, which were afterward averaged to derive $_{mean}TBR_{max}$ values to reflect the true metabolic activity and/or the inflamed state of fat tissue cells.

TABLE 1. PET-Related Data of the Study Population and the 2 Groups of Controls

	Patients		Controls	
PET Data	**Pre surgery**	**After surgery**	**BMI < 25**	**BMI ≥ 25 < 30**
n	10		7	5
Fasting glucose, mmol/L*	5.19 ± 0.32	5.13 ± 0.37	5.03 ± 0.49	5.3 ± 0.4
^{18}F-FDG dose injected, MBq*	83.4 ± 11.3	78.6 ± 5.03	78.1 ± 5.52	78.6 ± 3.51
^{18}F-FDG blood pool activity (jugular vein, $_{mean}SUV_{mean}$)*	1.10 ± 0.32	1.28 ± 0.57	1.18 ± 0.47	1.43 ± 0.12
Carotids ^{18}F-FDG uptake $_{mean}TBR_{max}$†	1.92 ± 0.35	1.23 ± 0.15	1.39 ± 0.21	1.30 ± 0.09
ΔCarotids $_{mean}TBR_{max}$	−0.69 ± 0.34 (−0.32 to −1.5)			
PAT ^{18}F-FDG uptake $_{mean}TBR_{max}$‡	1.34 ± 0.49	0.84 ± 0.08		
ΔPAT $_{mean}TBR_{max}$	−0.5 ± 0.47 (−0.03 to −1.67)			
VAT ^{18}F-FDG uptake $_{mean}TBR_{max}$§	0.65 ± 0.19	0.36 ± 0.11		
ΔVAT $_{mean}TBR_{max}$	−0.29 ± 0.19 (−0.03 to −0.67)			
SAT ^{18}F-FDG uptake $_{mean}TBR_{max}$‖	0.54 ± 0.3	0.44 ± 0.21		
ΔSAT $_{mean}TBR_{max}$	−0.1 ± 0.15 (−0.31 to 0.14)			
BAT ^{18}F-FDG uptake TBR_{max}‖	0.98 ± 2.08	2.44 ± 2.97		
ΔBAT $_{mean}TBR_{max}$	1.46 ± 2.76 (−1.5 to 7.33)			

Values are mean ± SD or n (%). ΔDifference over 1 year between pre surgery and postsurgery. BAT = brown adipose tissue, BMI = body mass index, MBq = megabecquerel, n.s. = not significant, PAT = pericardial adipose tissue, PET = positron emission tomography, SAT = subcutaneous adipose tissue, SD = standard deviation, TBR = target-to-background ratio, VAT = visceral adipose tissue.

* P = n.s. for patients pre surgery vs patients postsurgery, patients pre surgery vs both groups of controls, patients postsurgery vs both groups of controls, and between both groups of controls.

† $P < 0.0001$ for patients pre surgery vs patients postsurgery; $P = 0.002$ for patients pre surgery vs controls BMI < 25; $P = 0.001$ for patients pre surgery vs controls BMI ≥ 25 < 30; P = n.s. for patients postsurgery vs both groups of controls and between both groups of controls.

‡ $P = 0.008$.

§ $P = 0.001$.

‖ P = n.s.

Image Analysis of the Vessels

Image analysis of the vessels was performed on the same workstation as mentioned previously. The methodology for the analysis and the excellent reproducibility of the measurements has been previously reported.[23,24] Briefly, arterial ^{18}F-FDG uptake was quantified by drawing a ROI around each common carotid artery on every slice of the coregistered transaxial PET/CT images (Figure 2A and B). By averaging the SUV_{max} values of all arterial slices of the left and right common carotid, a $_{mean}SUV_{max}$ value was derived for the carotid arteries. The arterial TBR_{max} was calculated by normalizing the SUV_{max} for the ^{18}F-FDG blood pool activity by dividing the SUV_{max} value in the artery by the average blood mean SUV estimated from both JV as described earlier. The arterial TBR_{max} values were then averaged to derive a $_{mean}TBR_{max}$ for both carotid arteries. The TBR is considered to be a reflection of arterial ^{18}F-FDG uptake and reflective of underlying macrophage activity.[17]

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation and categorical data as absolute numbers and percentages. Normality of distribution of data was tested using the Kolmogorov–Smirnov test. Comparisons between continuous variables were performed with the independent or paired samples Student t test or the Mann–Whitney U test and correlations with the Pearson or Spearman correlation coefficient, wherever appropriate. Comparison between the groups of patients and controls was performed using analysis of variance with appropriate correction for multiple comparisons using Tukey post hoc testing.

Differences between the presurgical and postsurgical ^{18}F-FDG uptake in the carotids, the PAT, the VAT, the SAT, the BAT, and between the presurgical and postsurgical BMI are given as delta (Δ). All statistical analyses were performed using SPSS statistical package 16.0 (SPSS Inc, Chicago, IL).

RESULTS

Population Characteristics

Characteristics of the patients as well as the healthy 7 lean and 5 overweight volunteers are given in Table 2, and PET-related methodological data is given in Table 1.[15,19,20]

BMI

The BMI showed a highly significant decrease 1 year after BaS in the patient group (Table 2). No significant correlation was seen between preoperative and postoperative BMI values and all of the other respective ^{18}F-FDG uptake values in the

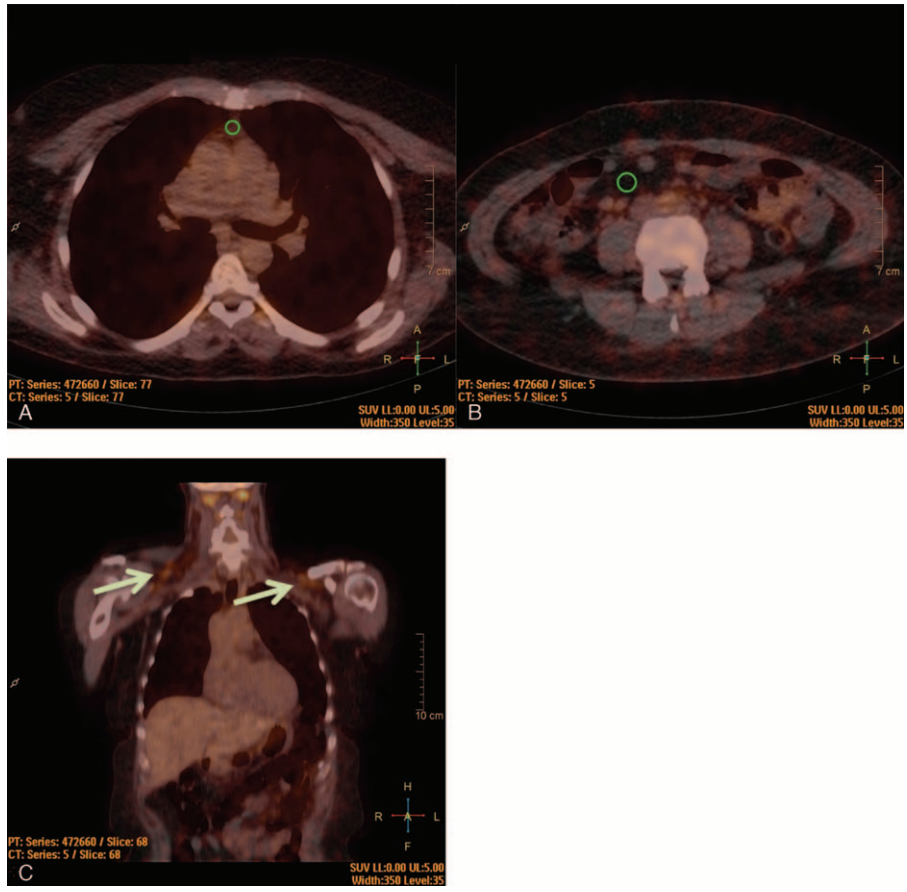

FIGURE 1. ^{18}F-FDG PET/CT image analysis of the (A) PAT, the (B) VAT, and (C) BAT. For PAT and VAT, standard ROIs (green) were placed on 3 consecutive slices whenever possible and SUV_{max} values across those slices were averaged. Afterward, $_{mean}SUV_{max}$ values were corrected for the ^{18}F-FDG uptake blood pool activity in the JVs to derive mean TBR ($_{mean}TBR_{max}$) of the ^{18}F-FDG uptake. PAT ROIs were placed in the substernal mediastinal region of the chest cranial of the heart to avoid an ^{18}F-FDG overspill from the myocardium or the thoracic vasculature. For VAT analysis, ROIs were placed in the abdominal visceral fat tissue above or below the kidneys to avoid overspill from the physiological ^{18}F-FDG uptake in the kidneys. (C) Typical localization of BAT in the shoulders (arrows) 1 year after BaS. In this patient, no BAT at all was observed before BaS (image not shown). As with PAT and VAT, SUV_{max} values of BAT were afterward corrected for blood pool activity in the JV to derive TBR_{max} values. ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, BaS = bariatric surgery, BAT = brown adipose tissue, JV = jugular vein, PAT = pericardial adipose tissue, PET/CT = positron emission tomography/computed tomography, ROI = region of interest, SUV_{max} = maximal standardized uptake value, TBR = target-to-background ratio, VAT = visceral adipose tissue.

carotids, the PAT, VAT, SAT, and the BAT, respectively (P = n.s. for all). Also, no significant correlation was observed between the ΔBMI and the ΔCarotids, ΔVAT, ΔPAT, ΔSAT, and ΔBAT $_{mean}TBR_{max}$, respectively (P = n.s. for all).

Vascular ^{18}F-FDG Uptake

In BaS patients, carotids $_{mean}TBR_{max}$ before surgery ($Carotids_{pre}$ $_{mean}TBR_{max}$) was significantly higher compared to the carotids $_{mean}TBR_{max}$ values in both groups of controls. However, patient's ^{18}F-FDG uptake in the carotids decreased 1 year after BaS leading to a significantly lower $Carotids_{post}$ $_{mean}TBR_{max}$ compared to the respective preoperative values (Table 1, Figure 3A). Accordingly, BaS patient's $Carotids_{post}$ $_{mean}TBR_{max}$ 1 year after surgery were not significantly different from the ^{18}F-FDG uptake parameters of the carotids in the 2 groups of controls (Table 1, Figure 3B). In BaS patients, the ^{18}F-FDG blood pool activity within the JV was not significantly different between the presurgical and postsurgical PET (Table 1). Additionally, there were no significant differences between patient's presurgical and postsurgical ^{18}F-FDG blood pool activity, respectively, and both groups of controls (Table 1).

PAT, VAT, and SAT ^{18}F-FDG Uptake

The metabolic activity of PAT and VAT considerably declined after BaS leading to a significantly lower PAT_{post} and VAT_{post} $_{mean}TBR_{max}$ compared with the respective preoperative values (Table 1, Figure 4A and B). Furthermore, a significantly positive correlation was seen between ΔPAT and ΔVAT $_{mean}TBR_{max}$ ($r = 0.674$, $P = 0.033$) and between ΔCarotids and ΔVAT $_{mean}TBR_{max}$ ($r = 0.644$, $P = 0.044$). Accordingly, a positive correlative trend between ΔCarotids and ΔPAT $_{mean}TBR_{max}$ ($r = 0.560$, $P = 0.093$) was observed. These findings are in contrast to the control measurements of the ^{18}F-FDG uptake in the SAT, which did not show a significant decline after BaS (Table 1). Furthermore, no significant correlation was found between ΔCarotids and ΔSAT $_{mean}TBR_{max}$, between ΔPAT and ΔSAT $_{mean}TBR_{max}$, and between ΔVAT and ΔSAT $_{mean}TBR_{max}$, respectively (P = n.s. for all).

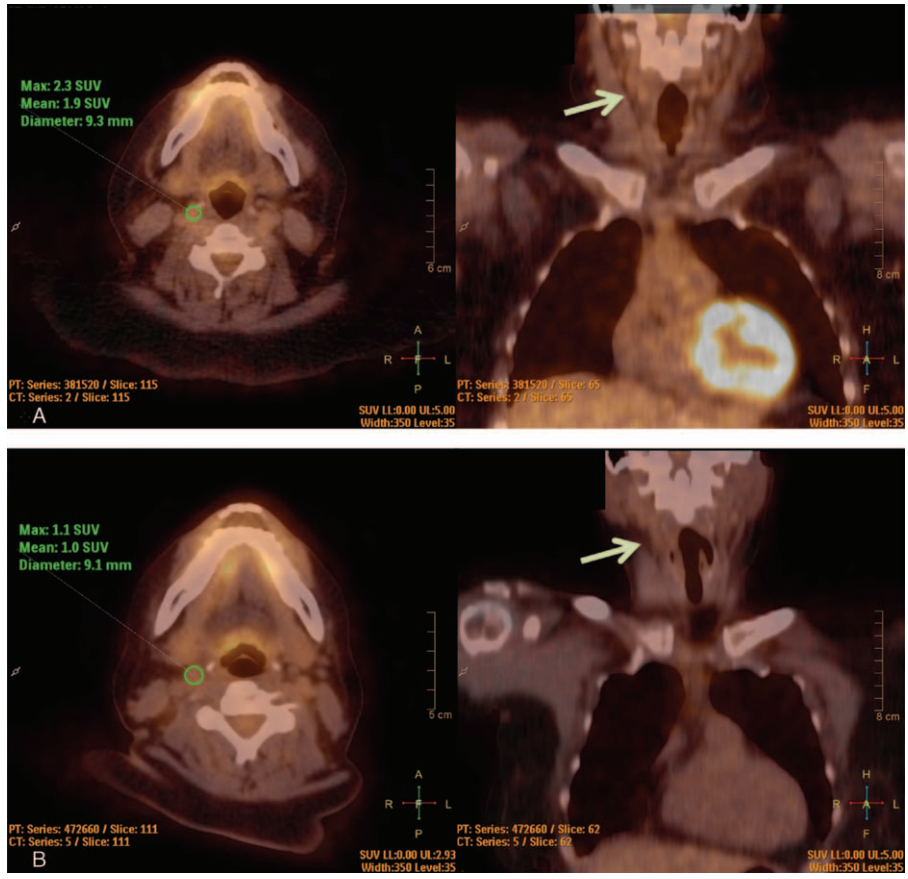

FIGURE 2. ^{18}F-FDG PET/CT image analysis of the carotid arteries (arrows) before and after BaS. ^{18}F-FDG PET/CT images of the neck in transaxial and coronal view (A) before and (B) after BaS. ROIs (green) drawn around the outer border of the vessel wall of the right common carotid artery (SUV_{max}, SUV_{mean}, and diameter of the ROIs) showing higher ^{18}F-FDG uptake values before BaS (SUV_{max} 2.3 vs SUV_{max} 1.1 after BaS). SUV_{max} values were corrected for the blood pool activity in the JVs to derive mean TBR ($_{mean}TBR_{max}$) values. ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, BaS = bariatric surgery, JV = jugular vein, PET/CT = positron emission tomography/computed tomography, ROI = region of interest, SUV_{max} = maximal standardized uptake value, TBR = target-to-background ratio.

No significant correlations were found between the $_{mean}TBR_{max}$ values in VAT and PAT as well as between any of the $_{mean}TBR_{max}$ values in the 3 adipose tissues and in the carotids preoperatively and postoperatively (P = n.s. for all). However, we found a significant correlation between the preoperative $_{mean}TBR_{max}$ values in the SAT and the respective $_{mean}TBR_{max}$ values in VAT ($r = 0.632$, $P = 0.05$) and PAT ($r = 0.786$, $P = 0.007$), respectively. In contrast, no significant correlation was found between the postoperative SAT $_{mean}TBR_{max}$ and the VAT and PAT $_{mean}TBR_{max}$, respectively (P = n.s.).

BAT Activity

Results regarding the BAT activity before and 1 year after BaS in the present patient population were previously published by our group.[19,20] Briefly, before surgery, a minimal cold-induced BAT activity in supraclavicular depots was observed in 2 females.[20] After BaS, BAT was seen in 5 of 10 subjects, including the 2 mentioned female subjects. Of these 5 BAT-positive patients, 1 subject was observed with an increased BAT activity, 3 previously BAT-negative subjects became BAT positive after surgery, and 1 subject showed a decreased BAT activity.[20]

We found a negative correlation between ΔPAT and ΔBAT $_{mean}TBR_{max}$ ($r = -0.755$, $P = 0.012$). A negative trend was observed between the ΔCarotids and the ΔBAT $_{mean}TBR_{max}$ ($r = -0.239$, $P = 0.506$) and between ΔVAT and ΔBAT $_{mean}TBR_{max}$ ($r = -0.593$, $P = 0.071$). No significant correlation was found between the ΔSAT and ΔBAT $_{mean}TBR_{max}$ (P = n.s.).

No significant correlations were seen between the preoperative and postoperative $_{mean}TBR_{max}$ values of VAT, PAT, and SAT and the respective preoperative and postoperative BAT $_{mean}TBR_{max}$ values (P = n.s. for all). Also, correlations between the preoperative and postoperative $_{mean}TBR_{max}$ values in the carotids and the respective BAT $_{mean}TBR_{max}$ values failed to show statistical significance (P = n.s. for all).

DISCUSSION

One year after BaS, ^{18}F-FDG uptake in carotid arteries was dramatically decreased reflecting a reduction in carotid artery inflammation. In addition, ^{18}F-FDG uptake in PAT and VAT significantly declined after BaS and, with regard to VAT, also showed a significant correlation with the diminished carotid wall inflammation. As was previously published by our group, BAT activity increased over the same time period.[19,20] The

TABLE 2. Characteristics of the Study Population and the 2 Groups of Controls

Characteristics	Patients		Controls	
	Pre surgery	After Surgery	BMI < 25	BMI ≥ 25 < 30
n	10		7	5
Age, y*	40 ± 9	41 ± 9	25 ± 4	26 ± 4
Sex				
Male	2 (20.0)	2 (20.0)	6 (85.7)	5 (100)
Female	8 (80.0)	8 (80.0)	1 (14.3)	0 (0)
Weight, kg†	127.3 ± 17.5 (98.2–155.0)	90.8 ± 16.5 (74.0–120.0)	77.6 ± 7.2 (70.3–90.3)	91.5 ± 4.7 (85.6–95.5)
Height, m‡	1.75 ± 0.09 (1.63–1.91)	1.75 ± 0.09 (1.63–1.91)	1.83 ± 0.06 (1.77–1.92)	1.84 ± 0.02 (1.82–1.88)
BMI§, kg/m^2	41.7 ± 4.34 (34.3–48.4)	29.7 ± 4.15 (24.3–35.9)	23.2 ± 1.20 (21.3–24.4)	27.1 ± 1.25 (25.9–28.6)
<25	0	1 (10.0)	7 (100)	0
≥25 < 30	0	3 (30.0)	0	5 (100)
≥30	10 (100)	6 (60.0)	0	0
ΔBMI	−12.0 ± 3.0 (−7.2 to −15.6)			

Values are mean ± SD or n (%). ΔDifference over 1 year between pre surgery and postsurgery. BMI = body mass index, n.s. = not significant, SD = standard deviation.

* $P = 0.001$ for patients pre surgery vs controls BMI < 25, and $P = 0.003$ for patients pre surgery vs controls BMI ≥ 25 < 30; $P < 0.0001$ for patients postsurgery vs controls BMI < 25, and $P = 0.002$ for patients postsurgery vs controls BMI ≥ 25 < 30.

† $P < 0.0001$ for patients pre surgery vs patients postsurgery, for patients pre surgery vs controls BMI < 25, and for patients pre surgery vs controls BMI ≥ 25 < 30; P = n.s. for patients postsurgery vs both groups of controls, and between both groups of controls.

‡ P = n.s. for patients vs both groups of controls, and between both groups of controls.

§ $P < 0.0001$ for patients pre surgery vs patients postsurgery, for patients pre surgery vs controls BMI < 25, and for patients pre surgery vs controls BMI ≥ 25 < 30; $P = 0.001$ for patients postsurgery vs controls BMI < 25; P = n.s. for patients postsurgery vs controls BMI ≥ 25 < 30 and between both groups of controls.

results of our study indicate a significant benefit within 1 year after BaS with regard to the degree of vascular inflammation and the metabolic activity in different adipose tissues. We hypothesize that these might contribute to the previously reported diminished cardiovascular risk in morbidly obese patients after BaS.[2,5,7–9]

Impressively, our study showed that the decrease in carotid inflammation could already be observed 1 year after BaS in otherwise healthy patients, indicating that vascular inflammation as part of atherosclerosis in obesity is reversible. Additionally, patients' declining carotid ^{18}F-FDG uptake reached even values comparable to normal weight subjects with a BMI < 25.

The SOS study showed that cardiovascular risk factor improvement requires a sustained and very large (10–40 kg) weight loss.[2,5] Accordingly, a mean weight loss of 36.5 kg was seen in our patient population 1 year after BaS, which might at least partly explain the highly significant decrease of the inflammatory changes in the carotids. However, in the surgery group of the SOS study, no significant association between weight loss and cardiovascular events could be detected.[2,5] This is in accordance with the results of our study as we also failed to show any significant impact of BMI or ΔBMI on not only the degree of carotid inflammation but also on the metabolic activity in VAT, PAT, and BAT. Since there was a rather fast and impressive decline of carotid artery inflammation without a direct correlation with the degree of weight loss, our findings indicate a potential weight loss independent effect of BaS. In line with this finding, it was previously observed that the relative expression and serum levels of interleukin-6 (IL-6), tumor necrosis factor (TNF-α), or C-reactive protein (CRP) were reduced 1 year after BaS but did not correlate with weight, BMI, and body fat.[5,27,28] We speculate that this effect might be related to ''direct'' anti-inflammatory effects of BaS as recently described.[27,28]

As with the diminished carotid inflammation, the ^{18}F-FDG uptake both in PAT and VAT significantly declined 1 year after BaS. The rationale for analyzing the metabolic activity in VATs by means of ^{18}F-FDG PET was related to the fact that volumetric measurements with CT or magnetic resonance imaging alone may not be sufficient and could be improved by using functional imaging with PET to determine the metabolic activity in fat tissue and its relation to the cardiovascular risk.[11,12,21,29] Furthermore, it is now well established that VAT is functionally more active than SAT and that its expansion, rather than that of SAT, confers a high risk for developing the metabolic syndrome as well as an increased incident of cardiovascular disease.[25,26] These differences might explain the higher ^{18}F-FDG uptake values in VAT than SAT in our study.[21] In accordance, we did not find neither a significant decline of the metabolic activity of SAT 1 year after BaS nor any correlation between the decline of the ^{18}F-FDG uptake in the carotids, in the PAT, and in the VAT and the increase of the metabolic activity of the BAT on the one hand and the delta of the SAT on the other hand. However, the underlying mechanisms are still not completely understood. In contrast, monocytes and monocyte-derived macrophages are well known to be the cellular hallmarks in the pathogenesis of atherosclerosis.[30] These macrophages seem also to play a significant role in inflammatory changes of adipose tissues. Animal studies demonstrated a specific contribution of certain monocyte subsets to atherogenesis and, additionally, an obesity-associated macrophage accumulation in adipose tissue.[31–34] As it is known that the ^{18}F-FDG uptake reveals a highly significant correlation with the degree of macrophage density in the arterial wall as depicted by histological CD 68 staining, it is not unlikely that ^{18}F-FDG uptake in adipose tissue is also attributed to the macrophage density of adipose tissues.[17] Therefore, our study seems to further support potentially inflammatory changes of

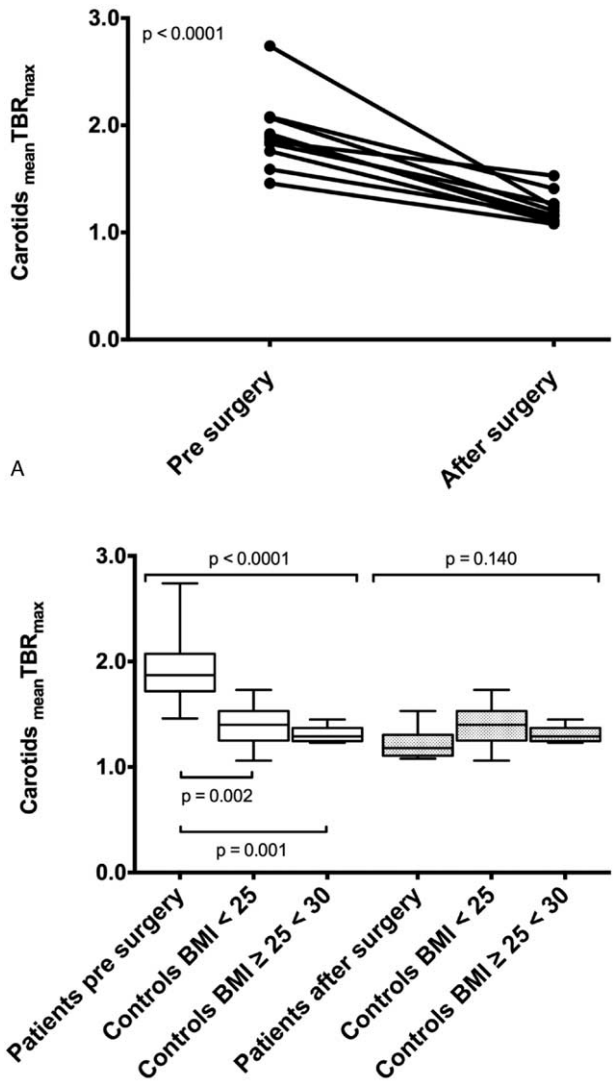

FIGURE 3. (A) Vascular ^{18}F-FDG uptake in the carotids in patients before and 1 year after BaS. (B) Comparison of the preoperative and postoperative vascular ^{18}F-FDG uptake between patients and the 2 groups of controls. Arterial ^{18}F-FDG uptake in the carotids ($_{mean}TBR_{max}$) significantly decreased 1 year after BaS (A). Patients' preoperative ^{18}FDG uptake in the carotids was significantly higher as compared to lean (BMI $<$ 25; $P = 0.002$) and overweight controls (BMI $\geq$ 25 $<$ 30; $P = 0.001$). One year after BaS, no significant differences between patients' carotids $_{mean}TBR_{max}$ compared with both groups of controls can be observed (B). ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, BaS = bariatric surgery, BMI = body mass index, TBR = target-to-background ratio.

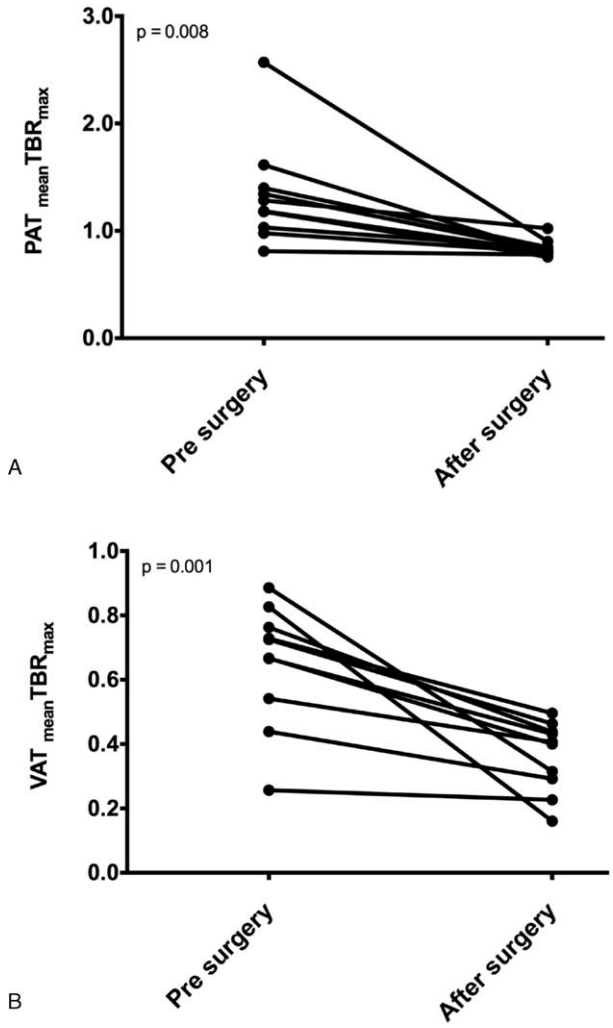

FIGURE 4. Comparison between the (A) PAT and the abdominal (B) VAT ^{18}F-FDG uptake of the patients before and 1 year after BaS. Both PAT and VAT $_{mean}TBR_{max}$ shows a highly significant decline over a time period of 1 year after BaS. ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, BaS = bariatric surgery, BMI = body mass index, PAT = pericardial adipose tissue, TBR = target-to-background ratio, VAT = visceral adipose tissue.

adipose tissues underlying the metabolic activity in PAT and VAT as depicted by the ^{18}F-FDG uptake.

Our study revealed interesting clues on the role of BAT on inflammatory changes in the carotid arteries 1 year after BaS. There is emerging evidence that activation of BAT increases energy expenditure and that obese and overweight subjects have lower BAT activity.[13,15,16,19,20] Moreover, animal studies and more recent clinical evidence argue that decreasing adiposity by activating BAT and potently oxidizing fatty acids would, in most settings, indirectly benefit the vasculature.[16,25,35] In fact, in humans, cervical BAT size is negatively correlated with BMI and the degree of coronary atherosclerosis.[35] BAT has therefore emerged as an attractive target for the treatment of obesity and associated cardiovascular disease.[16] In the current study, we observed a negative trend between the decline of carotid wall inflammation and the increase of BAT activity 1 year after BaS. It could thus be hypothesized that increasing BAT activity leads to an anti-inflammatory effect in the vasculature, as depicted by the decreasing ^{18}F-FDG uptake in the carotids. A fact, which might further elucidate the anti-inflammatory properties of BAT, is the significant association between the decline of the metabolic activity of PAT with the increase in BAT activity, which we observed after BaS. This might be explained by declining inflammatory changes in PAT due to the observed increase of BAT activity. This effect was previously described in an animal model with BAT-transplanted mice.[36]

Although some might argue that the limited number of patients in our study could hamper interpretation, we believe the number of patients to be sufficient because of the depth of our investigations combined with the fact that every person has been his/her own control. As we only included healthy patients and excluded all patients with any kind of comorbidities, only a limited number of patients was feasible for inclusion. This was mainly due to the fact that most of patients in question for inclusion suffered from diabetic or prediabetic disease. Furthermore, the patients group consisted of more females and much older subjects compared with the 2 groups of controls. Again, because every person has been his/her own control and the differences were the same before and after BaS, age and/or gender-related bias is unlikely.

As we applied an imaging protocol including cold stimulation appropriate to disclose BAT activity,[15,19,20] we could not take advantage of methods that have been employed to optimize the arterial ^{18}F-FDG signal, for example, a longer ^{18}F-FDG circulation time. However, the same imaging protocol was applied to the subjects in all groups. Furthermore, we, because of restrictions due to radiation protection of the patients, were not able to apply a weight-adapted FDG dose. Instead we chose a standard dose of the tracer. However, previously published data indicated no significant impact of the injected FDG dose on the degree of FDG uptake in the vasculature. In addition, we used TBR with for the underlying blood pool corrected SUV values of the carotids.[37] Therefore, the impact of the low FDG standard dose in the current study should not lead to a significant impact on our study results.

Obviously, we were not able to retain biopsies to compare histology of vascular and adipose tissues with the imaging parameters and have, with that regard, to rely on previously published data.[21,34]

Intentionally, we decided not to evaluate biomarkers in the patient group because of the known fact that inflammatory biomarkers such as CRP, IL-6, or TNF-α show significant, weight-independent reductions after BaS.[5,27,28] Therefore, repetitive evaluation of the biomarkers within the context of the current study would not have added any significant new information with that regard.

We demonstrated that in morbidly obese patients, the degree of carotid inflammation normalizes already 1 year after BaS. This is intriguing as our results indicate that vascular inflammation as part of the atherosclerotic disease process may be almost completely reversed, even within that rather short time period. This effect appeared not to be completely related to only the degree of weight loss per se and, intriguingly, one might speculate on anti-inflammatory effects induced by BaS itself. In addition, a significantly reduced metabolic activity of PAT and VAT as well as an increased degree of BAT was observed 1 year after BaS. We hypothesize the latter to possibly have contributed to the observed beneficial changes in vascular inflammation and the metabolic activity in PAT and VAT.

REFERENCES

1. Tirosh A, Shai I, Afek A, et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. *N Engl J Med.* 2011;364:1315–1325.
2. Sjöström L, Lindroos AK, Peltonen M, et al., Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med.* 2004;351:2683–2693.
3. James WP, Caterson ID, Coutinho W, et al., SCOUT Investigators. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med.* 2010;363:905–917.
4. Wing RR, Hill JO. Successful weight loss maintenance. *Annu Rev Nutr.* 2001;21:323–341.
5. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. *J Am Med Assoc.* 2012;307:56–65.
6. Nissen SE, Nicholls SJ, Wolski K, et al., STRADIVARIUS Investigators. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. *J Am Med Assoc.* 2008;299:1547–1560.
7. Christou NV, Sampalis JS, Liberman M, et al. Surgery decreases long-term mortality, morbidity, and health care use in morbidly obese patients. *Ann Surg.* 2004;240:416–423.
8. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med.* 2007;357:753–761.
9. Grundy SM. Obesity, metabolic syndrome, and coronary atherosclerosis. *Circulation.* 2002;105:2696–2698.
10. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature.* 2006;444:875–880.
11. Rosito GA, Massaro JM, Hoffmann U, et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation.* 2008;117:605–613.
12. Greif M, Becker A, von Ziegler F, et al. Pericardial adipose tissue determined by dual source CT is a risk factor for coronary atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2009;29:781–786.
13. Ouellet V, Labbe SM, Blondin DP, et al. Brown adipose tissue oxidative metabolism contributes to energy expenditure during acute cold exposure in humans. *J Clin Invest.* 2012;122:545–552.
14. Virtanen KA, Lidell ME, Orava J, et al. Functional brown adipose tissue in healthy adults. *N Engl J Med.* 2009;360:1518–1525.
15. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, et al. Cold-activated brown adipose tissue in healthy men. *N Engl J Med.* 2009;360:1500–1508.
16. Chang L, Villacorta L, Li R, et al. Loss of perivascular adipose tissue on peroxisome proliferator-activated receptor-γ deletion in smooth muscle cells impairs intravascular thermoregulation and enhances atherosclerosis. *Circulation.* 2012;126:1067–1078.
17. Tawakol A, Migrino RQ, Bashian GG, et al. In vivo ^{18}F-fluorodeoxyglucose positron emission tomography imaging provides a noninvasive measure of carotid plaque inflammation in patients. *J Am Coll Cardiol.* 2006;48:1818–1824.
18. Pedersen SF, Graebe M, Fisker Hag AM, et al. Gene expression and 18FDG uptake in atherosclerotic carotid plaques. *Nucl Med Commun.* 2010;31:423–429.
19. Vijgen GH, Bouvy ND, Teule GJ, et al. Brown adipose tissue in morbidly obese subjects. *PLoS One.* 2011;6:e17247.
20. Vijgen GH, Bouvy ND, Teule GJ, et al. Increase in brown adipose tissue activity after weight loss in morbidly obese subjects. *J Clin Endocrinol Metab.* 2012;97:E1229–E1233.
21. Christen T, Sheikine Y, Rocha VZ, et al. Increased glucose uptake in visceral versus subcutaneous adipose tissue revealed by PET imaging. *JACC Cardiovasc Imaging.* 2010;3:843–851.
22. von Elm E, Altman DG, Egger M, et al. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007;370:1453–1457.
23. Rudd JH, Myers KS, Bansilal S, et al. Atherosclerosis inflammation imaging with 18F-FDG PET: carotid, iliac, and femoral uptake reproducibility, quantification methods, and recommendations. *J Nucl Med.* 2008;49:871–878.
24. Bucerius J, Duivenvoorden R, Mani V, et al. Prevalence and risk factors of carotid vessel wall inflammation in coronary artery disease

patients: FDG-PET and CT imaging study. *JACC Cardiovasc Imaging*. 2011;4:1195–1205.

25. Hajer GR, van Haeften TW, Visseren FLJ. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J.* 2008;29:2959–2971.
26. Fitzgibbons TP, Kogan S, Aouadi M, et al. Similarity of mouse perivascular and brown adipose tissues and their resistance to diet-induced inflammation. *Am J Physiol Heart Circ Physiol.* 2011;301:H1425–H1437.
27. Viana EC, Araujo-Dasilio KL, Miguel GP, et al. Gastric bypass and sleeve gastrectomy: the same impact on IL-6 and TNF-α. Prospective Clinical Trial. *Obes Surg*. 2013;23:1252–1261.
28. Ruiz-Tovar J, Oller I, Galindo I, et al. Change in levels of C-reactive protein (CRP) and serum cortisol in morbidly obese patients after laparoscopic sleeve gastrectomy. *Obes Surg*. 2013;23:764–769.
29. Brunken R, Freire M, Neumann D. Visceral fat volume is unrelated to adipose tissue inflammation. *J Nucl Cardiol.* 2008;15:S7(Abstract).
30. Getz GS. Thematic review series: the immune system and atherogenesis. Immune function in atherogenesis. *J Lipid Res.* 2005;46:1–10.
31. Tacke F, Alvarez D, Kaplan TJ, et al. Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J Clin Invest.* 2007;117:185–194.
32. Swirski FK, Libby P, Aikawa E, et al. Ly-6Chi monocytes dominate hypercholesterolemia-associated monocytosis and give rise to macrophages in atheromata. *J Clin Invest.* 2007;117:195–205.
33. Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003;112:1796–1808.
34. Bucerius J, Mani V, Wong S, et al. Arterial and fat tissue inflammation are highly correlated: a prospective 18F-FDG PET/CT study. *Eur J Nucl Med Mol Imaging*. 2014;41:934–945.
35. Kortelainen ML. Association between cardiac pathology and fat tissue distribution in an autopsy series of men without premortem evidence of cardiovascular disease. *Int J Obes Relat Metab Disord.* 1996;20:245–252.
36. Gunawardana SC, Piston DW. Reversal of type 1 diabetes in mice by brown adipose tissue transplant. *Diabetes.* 2012;61:674–682.
37. Bucerius J, Mani V, Moncrieff C, et al. Optimizing 18F-FDG PET/CT imaging of vessel wall inflammation: the impact of 18F-FDG circulation time, injected dose, uptake parameters, and fasting blood glucose levels. *Eur J Nucl Med Mol Imaging*. 2014;41:369–383.